Upon entry of the above amendment, claims 7-9, 12-13, 18-20, 22 and 33 will be pending in the instant application. Claim 33 has been amended to clarify the invention. Claims 12-13, 18-20 and 22 have been amended to correct an obvious typographical error. No new matter has been added

Support for the amendments to claims 7-9 can be found at page 5 of the specification as originally filed.

Issue Under 35 U.S.C. §112, first paragraph

Claims 7-9, 12-13, 18-20, 22 and 33 stand rejected under 35 U.S.C. §112 first paragraph as allegedly not being enabling for the full scope of the defined markush groups of R_1 and R_2 and R_6-R_9. Applicants respectfully traverse this assertion.

Claim 7 and dependent claims 8-9, 12-13, 18-20 and 22 are directed to compounds in which R^1 and R^2 are independently hydrogen, cyano, halo, nitro, optionally substituted amino, C_{1-4} alkyl, trifluoromethyl, $-CO_2H$, CO_2C_{1-4} alkyl, $C(O)NHC_{1-4}$ alkyl, or C_{1-4}-alkoxy, or R_1 and R_2 combined together with the carbon atoms to which they are attached form an optionally substituted 6-membered aromatic ring; R_6 is optionally substituted alkyl, aryl, hetroaryl, cycloalkyl, aralkyl or heteroaralkyl; R_7 is hydrogen or methyl; R_8 is optionally substituted alkyl, aralkyl or heteroaralkyl; R_9 is hydrogen, optionally substituted alkyl, aralkyl, heteroaralkyl or alkanoyl; and R_{13} and R_{14} are independently hydrogen, hydroxy or optionally substituted C_{1-4} alkyl. Claim 33 is directed to a pharmaceutical composition thereof.

According to the Examiner, "R1-R2 and R6-R9 is not enabled to be the entire scope as claimed (more specifically the terms optionally substituted, heterocyclic, aryl and heteroaryl groups)... [and] the instant claims were only enabled where R13 and R14 being only H- not the full scope as claimed." The Examiner maintains that because, "12 different heterocyclic, aryl and heteroaryl groups are represented that does not mean that Applicant is enabled for the entire scope of the claims." Applicants respectfully disagree for at least the following reasons.

Applicants respectfully note that, "[f]or a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation." MPEP 2164.02

The claimed genus is supported by the general method of production of compounds applicable to the genus as a whole (see *e.g.*, Examples 9 and 10 at pages 48-50 of the specification as originally filed); and specific examples of compounds that fall within the general

formula, which were made using a method of production that falls within the general method of production (see *e.g.*, Example 11 at pages 50-53 of the specification as originally filed). Therefore, based on this disclosure of representative examples, one of skill in the art would expect that the claimed genus of compounds could be made and used in the same manner as the representative examples without undue experimentation.

Regarding Dr. Dorwald's comment on the unpredictability of organic chemistry, Applicants note that, "[t]he scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required." MPEP 2164.03

For the aforementioned reasons, Applicants respectfully submit that claims 7-9, 12-13, 18-20, 22 and 33 are enabled, and request withdrawal of the 35 U.S.C. §112 rejection.

Issue Under 35 U.S.C. §102(b)

Claims 1, 2, 3, 7, 8, 9, 11 and 33 stand rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Ogawa '113 (WO 94/01113A1). Applicants respectfully traverse this assertion. Applicants note that claims 1, 2 and 3 were not pending, therefore their rejection is moot.

Ogawa '113 discloses a series of benzene derivatives. Throughout the disclosure tetrahydroquinoline derivatives are exemplified. However, Ogawa '113 only discloses one perhydroquinoline derivative (compound 2-149, at page 146, which was cited by the Examiner). Applicants respectfully submit that the compounds exemplified in Ogawa '113 do not anticipate the amended claim scope because Ogawa neither discloses nor suggests compounds in which R_6 is optionally substituted aryl, wherein said aryl is optionally substituted by one to four substituents such as halo, hydroxy, alkoxy, alkanoyl, alkanoyloxy, optionally substitued amino, thiol, alkylthio, nitro, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, alkylthiono, alkyl- and arylsulfonyl, sulfonamido and heterocycloyl.

Applicants respectfully request withdrawal of the 35 U.S.C. §102(b) rejection.

Issue Under 35 U.S.C. §103(a)

Claims 18, 19, 20, 22 and 33 stand rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Matsumoto '199 (WO 2003/029199). Applicants respectfully traverse this assertion.

The compounds of the invention are inhibitors of 11β-hydroxysteroid dehydrogenase type 1 reductase activity, and are discussed above.

Matsumoto '199 discloses a series of benzene derivatives which contain three substituents: a urea group, a carbonyl group and a large ether group, and have vanilloid receptor agonist activity and are useful as analgesics or agents for treating urinary frequency or urinary incontinence. Example 396, on page 117 discloses a perhydroquinoline carbonyl group

with an ether group ortho to the carbonyl group, and a urea group meta to the carbonyl group. According to the Examiner, "Matsumoto differs from the instant application at the position of W: Applicant's –NR5Z at the 3'-position versus Applicant's 4-position."

Applicants respectfully submit that the compounds exemplified in Matsumoto neither disclose nor suggest compounds wherein W is $-NR_5C(O)R_8$, $NR_5C(O)OR_8$, $-NR_8C(O)NR_8R_7$, $-NR_5C(S)NR_8R_7$, $-NR_5S(O)_2R_8$, $-NR_8R_8$, $-C(O)NR_8R_7$, or $-OC(O)NR_8R_7$. "[I]n order to find a *prima facie* case of unpatentability in such instances [i.e., in chemical cases], a showing that the 'prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention' was also required..." and that "...in cases involving new chemical compounds, it remains ***necessary*** to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound." (Takeda Chemical Industries, Ltd. v. Alphapharm PTY., Ltd. 83 U.S.P.Q.2D 1169 (Fed. Cir. 2007)). According to the Court in Eisai v. Dr. Reddy's Laboratories (533 F.3d 1353 (Fed. Cir. 2008)), "post-KSR, a *prima facie* case of obviousness for a chemical compound still, in general, begins with a reasoned identification of a lead compound."

The Examiner has failed to point to any teaching in Matsumo which would have led one of ordinary skill in the art to modify a known compound in a particular manner, e.g., substitute a benzene ring at the 3'-position versus the 4-position. Rather than identify predictable solutions for treatment of diseases such as type-2 diabetes, the prior art disclosed a broad selection of compounds useful as analgesics or agents for treating urinary frequency or urinary incontinence, any one of which could have been selected as a lead compound for further investigation.

Furthermore, Applicants respectfully direct the Examiner to the Federal Circuit case Princeton Biochemicals, Inc. v. Beckman Coulter, Inc., which held:

> In making the assessment of differences between prior art and the claimed subject matter, section 103 specifically requires consideration of the claimed invention "as a whole."...Without this important requirement, an obviousness assessment might successfully break an invention into its component parts, then find a prior art reference corresponding to each component...This line of reasoning would import hindsight into the obviousness determination by using the invention as a roadmap to find its prior art components.

411 F.3d 1332 (Fed. Cir. 2005). Applicants submit that the Examiner has used hindsight to identify prior art corresponding to individual aspects of the invention (*e.g.*, a urea group, a carbonyl group and a large ether group) and has not pointed to any suggestion or motivation either in Matsumo, or in the knowledge generally available to one of ordinary skill in the art, to combine the reference teachings to provide the compounds of the instant invention.

Applicants respectfully request withdrawal of the 35 U.S.C. §103(a) rejection.

Conclusion

Applicants have addressed each and every issue set forth by the Examiner. Applicants respectfully submit that the present application is in good condition for allowance. Applicants have not amended the claims to cause the Examiner to perform additional searching and respectfully request consideration of the outstanding Final rejection and enter a Notice of Allowance.

If the Examiner believes for any reason that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (617) 871-4125.

If necessary, the Commissioner is hereby authorized in this, concurrent, and further replies, to charge payment or credit any overpayment to Deposit Account No. 50-4409 for any additional fees under 37 C.F.R. §1.16 or under 37 C.F.R. §1.17; particularly extension of time fees.

Respectfully submitted,

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